REMARKS

Claims 1-2, 4-5, 29, and 34-36 are pending in the present application. Claims 6-7, 9-21, 25, 27-28, and 30-33 remain withdrawn from consideration as allegedly being drawn to non-elected subject matter. The present Communication includes no amendments and thus does not introduce any new matter. Its entry is respectfully requested. Upon entry of the present Communication, claims 1-2, 4-5, 29, and 34-36 will remain pending and under examination.

The August 31, 2009 Office Action

Office Action's Rejection Under 35 U.S.C. §103 (Alvira)

Claims 1, 2, 4, 5, 29, and 34-36 were rejected under 35 USC 103(a), as allegedly unpatentable over the previously cited Alvira reference. According to the Office Action, "Alvira teaches the separation of R-equol from the S-equol, which meets the limitation of a composition comprising R-equol." The Office Action further stated that "Alvira teaches cyclodextrin (carrier) is used in separation process" and that "R-equol is the only required component for the composition claims." The Office Action acknowledged that Alvira does not teach that the combination of equol and cyclodextrin is pharmaceutical, but stated "in a claim drawn to a composition a statement to intended use (pharmaceutical) has little patentable significance." The Office Action further asserted that, "[i]n addition, it is well known that cyclodextrin can be used in pharmaceutical compositions which makes it obvious to manufacture the combination of equol and cyclodextrin." The Office Action further asserted that Alvira teaches all that is recited in

claims 4 and 5 except for the R-equol being present in 90 or 96% enantiomeric purity. In the opinion expressed in the Office Action, an artisan provided the technique of Alvira would have been able to optimize the purity of R-equol through routine experimentation even to the level of 90 or 96% purity. The Office Action further asserted that "Alvira teaches all that is recited in claim 29 except for the specified conjugates" and that "in the absence of unexpected data, it would have been obvious to employ any conjugated [sic] of the instant equol including those recited in the instant claims." The Office Action then concluded that one would have been motivated to do this "because equol and conjugates thereof would have been expected to have been equally effective."

In response, Applicants respectfully traverse the rejection. Alvira does not teach or suggest any pharmaceutical composition; any composition "consisting essentially of" the R enantiomer of equol (R-equol) and a pharmaceutically acceptable adjuvant, carrier or excipient; any composition comprising enantiomerically pure R-equol as an active agent; or any composition formulated for oral consumption or topical application comprising R-equol wherein the composition is substantially free of S-equol. Alvira does not provide a reason or motivation to prepare such compositions, nor any suggestion that it would be desirable or even feasible to do so. In fact, contrary to the contention expressed in the Office Action, Alvira does not even teach the separation of R-equol from S-equol. No description of a process or method of achieving such separation is provided. Indeed, Alvira does not even teach how one would obtain *racemic* equol, which was not readily available at the time, for further separation into individual enantiomers.

Rather, Alvira refers to "theoretical studies" using models based on molecular mechanics, and specifically notes that solvation and other effects would need to be studied to understand "real systems." No actual composition, including any presently claimed by Applicants is prepared or even suggested by Alvira. Furthermore, there is no indication that enantiomeric equol even could be produced or obtained in quantities that would prove useful in formulating compositions such as those claimed by Applicants. Thus, for at least these reasons, Alvira cannot render obvious Applicants' present claims.

Moreover, Applicants believe the Office Action has erred in asserting that the terms "pharmaceutical" and "for oral consumption or topical application," in the contexts in which they are used, merely refer to intended uses and thus have little or no patentable significance. For decades, the Office has recognized that claims to compounds and claims to pharmaceutical compositions are patentably distinct. In addition, the Court of Appeals for the Federal Circuit addressed a similar question in *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003), stating that an Applicant " ... might fashion a claim to cover the [prior art] metabolite in a way that avoids anticipation. For example, the metabolite may be claimed ... as a pharmaceutical composition." Thus, even a metabolite which was inherently disclosed in the prior art teaching its parent compound was patentably distinct from a pharmaceutical composition claiming it. Similarly, therefore, in the present case, even if Alvira had taught a method of obtaining individual enantiomers of equol (which it has not), its failure to mention or suggest any pharmaceutical, oral, or topical compositions containing the additional components

recited in the bodies of Applicants' claims, renders the reference insufficient to preclude patentability of such claims.

Furthermore, the Office has failed to properly evaluate the clear evidence of unexpected results provided in the previously submitted Rule 132 Declaration. In that regard, the Office Action stated that "[a]lthough the declaration provides different results for the R-equol with respect to the S-equol and the racemic, Alvira has already shown that the R and S isomers of equol are resolvable. For this reason, Alvira reads on instant claims drawn to a composition consisting essentially of R-equol plus cyclodextrin."

In traversing this aspect of the rejection, Applicants reiterate that Alvira has not in fact "shown that the R and S enantiomers of equol are resolvable." What Alvira has done is present theoretical calculations in an effort to study intermolecular forces, while specifically acknowledging that its methods do not reflect "real systems" that include actual solvents or that result in successful separation techniques. Moreover, the Office Action's rejection is based on an assertion of obviousness and thus acknowledges that Alvira does not specifically disclose the claimed compositions. Therefore, the demonstration of unexpected results previously presented still renders the present claims patentable over this art.

Applicants also note that contrary to the Office Action's statement, the pertinent issue is not whether the individual enantiomers of equol and its racemate behave differently from each other, but rather that the Applicants have demonstrated unexpected results over the art. In that regard, the evidence provided in the Declaration reveals that each of the R- and S- isomers of

equol exhibits properties that one of ordinary skill in the art could not have predicted. Applicants refer to the detailed discussion of these results provided in previously filed papers.

In light of the above, therefore, and the previously presented comments and evidence, Applicants maintain that the Office Action's obviousness rejection over Alvira is improper. Thus, Applicants respectfully request its reconsideration and withdrawal.

Office Action's Rejection Under 35 U.S.C. §102 (Widyarini)

Claims 1 and 2 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Widyarini, et al (Isoflavonoid Compounds from Red Clover (*Trifolium pratense*) Protect from Inflammation and Immune Suppression Induced by UV Radiation, Photochemistry and Photobiology, 2001, 74(3), pp. 465-470). According to the Office Action, the reference teaches isoequol (R-equol) in a lotion (carrier), and that the lotion can be applied topically to treat inflammation (pharmaceutical application).

In response, Applicants respectfully traverse the rejection. Applicants first point out that for a prior art reference to anticipate (or render obvious) a claimed invention, the prior art reference must enable a person of ordinary skill in the art to make and use the claimed invention. (See, e.g., *In re Kumar*, 418 F.3d 1361 (Fed. Cir. 2005) and *Impax Labs. v. Aventis Pharmaceuticals, Inc.* (Fed. Cir. 2008)). Thus, for the rejection to be proper, the prior art must enable the claimed invention.

Applicants' rejected claims 1 and 2 are directed to a pharmaceutical composition

consisting essentially of the R enantiomer of equol (R-equol) and a pharmaceutically acceptable adjuvant, carrier or excipient, and to the same composition wherein the composition is made by isolating R-equol from a racemic mixture of S-equol and R-equol. Widyarini does not sufficiently enable one of only ordinary skill in the art to make and/or use such compositions. Equol was not readily available at the time the Widyarini reference was published, and while the reference refers to "equol" and "isoequol" and suggests these are S- and R-equol, respectively, the reference sets forth no specific process that could be used to synthesize them, nor any method of otherwise obtaining them. Furthermore, there are references to "purified" samples, but no indication of how such samples might have been "purified" and no description of any degree of purification that might have been achieved. There are simply no steps whatsoever provided by the authors of the paper that could enable one of ordinary skill in the art to make Applicants' compositions as claimed.

Even more significantly, a simple reading of the reference reveals that it is not at all clear that the authors even were working with equol enantiomers. In that regard, the paper states the following:

> [m]etabolites of orally consumed isoflavones are produced by the gastrointestinal microflora and result in an additional array of metabolites that are currently being identified and characterized. **These include equol [(S)-4',7-dihydroxyisoflavane] and its related compound isoequol [(R)-enantiomer of (S)-equol]** . . . (Widyarini, p. 465, emphasis added).

Similarly, at page 466, the paper again refers to "the metabolites equol and isoequol" and purports to use these "metabolites," as well as others, in lotions. However, it is now known (as

the present specification and recent studies make clear) that R-equol is not a metabolite and is not "produced by the gastrointestinal microflora" upon oral consumption of isoflavones. While S-equol can, in some cases, and under certain conditions, be obtained as a metabolite, R-equol cannot and is not present in nature. Accordingly, the authors do not appear to even understand what materials they had in their possession, despite referring to them as R- and S-equol. What is certain, however, is that their claim to have been evaluating the "metabolite" R-equol cannot be true. Given this clear misunderstanding of the biology of equol, and the failure to provide any concrete process steps for obtaining the materials referred to therein, the Widyarini reference cannot be reasonably relied upon for any of its purported teachings, especially with respect to what is has deemed to be R-equol. Therefore, the Widyarini reference clearly does not enable one of ordinary skill in the art to produce a composition "consisting essentially of the R enantiomer of equol (R-equol) and a pharmaceutically acceptable adjuvant, carrier or excipient" as Applicants have claimed.

Simply put, an ordinarily skilled artisan following the teachings of Widyarini could not produce Applicants' claimed subject matter. Accordingly, the Widyarini reference does not enable the Applicants' claims and thus cannot anticipate them. For at least these reasons, therefore, the rejection under 35 U.S.C. §102(b) is improper and thus, Applicants respectfully request its reconsideration and withdrawal.

Office Action's Rejection Under 35 U.S.C. §103 (Widyarini)

Claims 4, 5, 29 and 34-36 were rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Widyarini, et al., alone, as applied to claims 1 and 2 above. According to the Office Action, the reference teaches all that is recited in claims 4, 5, 29, and 34-36, except for the purity level of the R-equol in the composition and the specified conjugates. The Office Action has concluded that an ordinarily skilled artisan would have been able to optimize the purity of R-equol through routine experimentation and that without unexpected results, it would have been obvious to employ any conjugated forms of equol and such conjugates would have been expected to be equally effective as the equol itself. (Applicants note the Office Action has offered no technical reasoning to support such assertions.)

In response, Applicants respectfully traverse the rejection. First, Applicants refer to and reiterate the comments set forth above concerning the Widyarini reference's failure to enable the present claims. For at least the reasons provided above in connection with the anticipation rejection, therefore, the obviousness rejection also is improper. Moreover, because the Widyarini reference does not teach a process that in fact can result in R-equol, or any other means of obtaining it, Widyarini cannot teach a method of optimizing the purity of R-equol to any degree, let alone the specific purity values recited in the rejected claims to which the Office Action refers. Similarly, because the reference fails to enable the claimed R-equol compositions, it also necessarily fails to enable the claimed conjugates of such compositions. Accordingly, like the anticipation rejection, the Office Action's obviousness rejection also is improper and thus, its

reconsideration and withdrawal are respectfully requested.

In view of the above remarks, Applicants believe all of the concerns set forth in the August 31, 2009 Office Action have been fully overcome and the claims are in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite such allowance.

Respectfully submitted,

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